	L #	Hits	Search Text	DBs	Time Stamp
1	L1	165	carboxylesterase$1	USPAT; US-PGPUB	2002/05/17 15:45
2	L2	4540	cpt-11 or (cpt adj "11") or apc	USPAT; US-PGPUB	2002/05/17 15:46
3	L3	773	camptothecin	USPAT; US-PGPUB	2002/05/17 15:46
4	L4	28	1 same (2 or 3)	USPAT; US-PGPUB	2002/05/17 15:46

PGPUB-DOCUMENT-NUMBER: 20020049324
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020049324 A1

TITLE: Aromatic esters of camptothecins and methods to treat cancers

PUBLICATION-DATE: April 25, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Cao, Zhisong	Friendswood	TX	US	
Giovanella, Beppino C.	Houston	TX	US	

US-CL-CURRENT: 546/48

ABSTRACT:

Aromatic camptothecin ester compounds having the formula: 1

are described as well as formulations containing the compounds. Methods of treating cancer and/or tumors are also disclosed.

DATE FILED: December 22, 2000

---------- KWIC ---------

BSTX:
[0029] Conversion of the prodrugs to camptothecins is mediated by a group of enzymes called esterases. Mammalian **carboxylesterases** represent a multigene family and are present in a wide variety of organs and tissues of many mammalian species (Satoh, in reviews in Biochemical Toxicology, 8:155-81, New York: Elsevier, 1987; Heymann, in Enzymatic Basis of Detoxication, 2:291-323, New York: Academic, 1980, and in Metabolic Basis of Detoxication, 1:229-45, New York: Academic, 1982). In general, the highest hydrolase activity occurs in the liver. **Carboxylesterase** activity is present in many tissues in addition to liver. More information about distribution of **carboxylesterases** in tissues can be found in a review article written by Satoh et al. (Annu. Rev. Pharmacol. Toxicol. 38, 257, 1998). **Carboxylesterases** are known to be responsible for the hydrolysis of many exogenous compounds, the consequences of which include both activation of prodrugs and deactivation of drugs. **CPT-11,** a semisynthetic **camptothecin** derivative and now commercially available for cancer treatment, is a prodrug of SN-38. This compound is converted to SN-38 by **carboxylesterases** (Danks et al., Cancer Res. 58, 20, 1998; Potter et al., Cancer Res. 58, 2646, 1998; Tsuji et al., J. Pharmacobio-Dyn. 14, 341, 1991). The prodrugs disclosed by the present invention are rapidly distributed throughout the body within a short period of time after delivery and are then converted to active

camptothecin compounds by **carboxylesterases** specifically in tissues.

PGPUB-DOCUMENT-NUMBER: 20020006379
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020006379 A1

TITLE: Production and use of novel peptide-based agents for use with bi-specific antibodies

PUBLICATION-DATE: January 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hansen, Hans J.	Slidell	LA	US	
Griffiths, Gary L.	Morristown	NJ	US	
Leung, Shui-On	Shatin	NT	US	
McBride, William J.	Summit	NJ	US	
Qu, Zhengxing	Warren	NJ	US	

US-CL-CURRENT: 424/1.49,424/178.1 ,435/5

ABSTRACT:

The present invention relates to a bi-specific antibody or antibody fragment having at least one arm that is reactive against a targeted tissue and at least one other arm that is reactive against a linker moiety. The linker moiety encompasses a hapten to which antibodies have been prepared. The antigenic linker is conjugated to one or more therapeutic or diagnostic agents or enzymes. The invention provides constructs and methods for producing the bispecific antibodies or antibody fragments, as well as methods for using them.

DATE FILED: April 3, 2001

---------- KWIC ---------

DETX:
[0126] The prodrug **CPT-11** (irinotecan) is converted in vivo by **carboxylesterase** to the active metabolite SN-38. One application of the invention, therefore, is to use a bsAb targeted against a tumor and a hapten (e.g. di-DTPA) followed by injection of a di-DTPA-**carboxylesterase** conjugate. Once a suitable tumor-to-background localization ratio has been achieved, the **CPT-11** is given and the tumor-localized **carboxylesterase** serves to convert **CPT-11** to SN-38 at the tumor. Due to its poor solubility, the active SN-38 will remain in the vicinity of the tumor and, consequently, will exert an effect on adjacent tumor cells that are negative for the antigen being targeted. This is a further advantage of the method. Modified forms of **carboxylesterases** have been described and are within the scope of the invention. See, e.g., Potter et al., Cancer Res. 58:2646-2651 (1998) and Potter et al., Cancer Res. 58:3627-3632

(1998).

DETX:
[0127] Etoposide is a widely used cancer drug that is detoxified to a major extent by formation of its glucuronide and is within the scope of the invention. See, e.g., Hande et al. Cancer Res. 48:1829-1834 (1988). Glucuronide conjugates can be prepared from cytotoxic drugs and can be injected as therapeutics for tumors pre-targeted with mAb-glucuronidase conjugates. See, e.g., Wang et al. Cancer Res. 52:4484-4491 (1992). Accordingly, such conjugates also can be used with the pre-targeting approach described here. Similarly, designed prodrugs based on derivatives of daunomycin and doxorubicin have been described for use with **carboxylesterases** and glucuronidases. See, e.g., Bakina et al. J. Med Chem. 40:4013-4018 (1997). Other examples of prodrug/enzyme pairs that can be used within the present invention include, but are not limited to, glucuronide prodrugs of hydroxy derivatives of phenol mustards and beta-glucuronidase; phenol mustards or **CPT-11** and carboxypeptidase; methotrexate-substituted alpha-amino acids and carboxypeptidase A; penicillin or cephalosporin conjugates of drugs such as 6-mercaptopurine and doxorubicin and beta-lactamase; etoposide phosphate and alkaline phosphatase.

PGPUB-DOCUMENT-NUMBER: 20010008939
PGPUB-FILING-TYPE: new-utility
DOCUMENT-IDENTIFIER: US 20010008939 A1

TITLE: Camptothecin derivatives having antitumor activity

PUBLICATION-DATE: July 19, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Penco, Sergio	Milan		IT	
Merlini, Lucio	Milan		IT	
Carminati, Paolo	Pomezia (Rome)		IT	
Zunino, Franco	Milan		IT	

US-CL-CURRENT: 546/41

ABSTRACT:

Camptothecin derivatives of camptothecin of formula (I) 1

wherein the groups R.sub.1, R.sub.2 and R.sub.3 are as defined in the description are disclosed.

The compounds of formula (I) are endowed with antitumor activity and show a good therapeutic index.

Processes for the preparation of the compounds of formula (I) and their use in the preparation of medicaments useful in the treatment of tumors, viral infections and antiplasmodium falciparum are also disclosed.

DATE FILED: December 22, 2000

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
EP	99 830 124.6	1999EP-99 830 124.6	March 9, 1999

---------- KWIC ---------

BSTX:
[0007] Water-soluble Irinotecan was approved for the treatment of many solid tumors and ascites (colon-rectum, skin, stomach, breast, small and non-small cell lung, cervix and ovarian cancer and in non-Hodgkin lymphoma). Moreover, Irinotecan resulted active in solid tumors resistant to Topotecan, vincristine or melphalan and MDR-1 cells resulted marginally resistant to the drug. The active metabolite was identified as the 10-hydroxyderivatives (SN-38), produced

by the action of **carboxylesterases**. **CPT-11** showed a good activitv using different administration routes, such as intraperitoneal, intravenous, oral (Costin D., Potmhexyl M. Advances in Pharmacol. 29B, 51-72 1994).

BSTX:
[0015] In fact, it was observed that some resistant tumour cells contain mutant forms of topo I, accordingly the formation of the topo I-DNA complex is damaged or some cells lack in the **carboxylesterase** activity, necessary for converting **CPT-11** in the active metabolite SN-38 and are thus resistant against this drug (Rothenberg, 1997, ibid.).

US-PAT-NO: 6361774
DOCUMENT-IDENTIFIER: US 6361774 B1
TITLE: Methods and compositions for increasing the target-specific toxicity of a chemotherapy drug
DATE-ISSUED: March 26, 2002
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Griffiths; Gary L.	Morristown	NJ	N/A	N/A
Hansen; Hans J.	Slidell	LA	N/A	N/A

US-CL-CURRENT: 424/178.1,424/179.1 ,424/181.1 ,424/9.1 ,530/391.1
ABSTRACT:

A method for increasing the target-specific toxicity of a drug is effected by pretargeting an enzyme to a mammalian target site, and then administering a cytotoxic drug known to act at the target site or a prodrug form thereof which is converted to the drug in situ, which drug is also detoxified to form an intermediate of lower toxicity using said mammal's ordinary metabolic processes, whereby the detoxified intermediate is reconverted to its more toxic form by the pretargeted enzyme and thus has enhanced cytotoxicity at the target site. Further enhancement can be achieved by pretargeting an enzyme which converts the prodrug to the cytotoxic drug at the target site. Kits for use with the method also are provided. The method and kits permit lower doses of cytotoxic agents, maximize target site activity and minimize systemic side effects.

7 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: September 17, 1999

---------- KWIC ---------

BSPR:
The prodrug **CPT-11** (irinotecan) is converted in vivo by **carboxylesterase** to the active metabolite SN-38. One application of the invention, therefore, is to use a bsMAb targeted against a tumor and a hapten (e.g. DTPA) followed by injection of a DTPA-carboxyl esterase conjugate. Once a suitable tumor-to-background localization ratio has been achieved, the CPT11 is given and the tumor-localized **carboxylesterase** serves to convert **CPT-11** to SN-38 at the tumor. Since the active SN-38 is poorly soluble it will remain in the vicinity of the tumor and, since it is being generated in the vicinity of the tumor, it is able to exert an effect on adjacent tumor cells that are negative for the antigen being targeted. These are further advantages of the method. Modified forms of **carboxylesterase** that can be expressed by cells have been described (Potter et al., Cancer Res., 58:2646-2651 and 3627-3632, 1998), and such designed enzymes are within the scope of the invention.

BSPR:
Etoposide is a widely used cancer drug that is detoxified to a major extent by

formation of its glucuronide (Hande et al., Cancer Res., 48: 1829-1834, 1988), and could therefore be used within the scope of the invention. Glucuronide conjugates can be prepared from cytotoxic drugs and be injected as therapeutics for tumors pre-targeted with MAb-glucuronidase conjugates (Wang et al., Cancer Res., 52:4484-4491, 1992). Accordingly, such conjugates can also be used with the bsMAb approach described here. Designed prodrugs based on derivatives of daunomycin and doxorubicin have been described (Bakina et al., J. Med Chem., 40:4013-4018, 1997) for use with **carboxylesterases** and glucuronidases, and these can be used within the scope of the invention. Some other combinations of prodrugs and enzymes that can be used within the invention are listed. Glucuronide prodrugs of hydroxy derivatives of phenol mustards (Schmidt et al., Bioorg. Med Chem. Lett., 7:1071-1076, 1997) and beta-glucuronidase. Phenol mustards or **CPT-11** and carboxypeptidase. Methotrexate-substituted alpha-amino acids and carboxypeptidase A. Beta-lactamase and penicillin or cephalosporin conjugates of drugs such as 6-mercaptopurine and doxorubicin. Alkaline phosphatase and etoposide phosphate.

BSPR:
The clearance characteristics of drugs can be modulated by certain agents, and the use of such modulating agents within the invention form an additional embodiment. For example, **CPT-11** clearance properties have been shown to be modulated by administration of cyclosporin A with the latter reducing the level of biliary clearance of SN-38 and its glucuronide (SN-38G) (Gupta et al., Cancer Res. 56:1309-1314, 1996). In turn, this raised the plasma concentration of SN-38G. This would allow for greater contact with tumor-targeted DTPAglucuronidase in the present invention. Gupta et al. also showed a similar effect when using phenobarbitol (Cancer Chemother. Pharmacol., 39:440-444, 1997), and thus, this agent could also be given along with **CPT-11** after pre-targeting DTPA-glucuronidase. In the latter article they also showed that pretreatment of rats with valproic acid (an inhibitor of uridine diphosphate glucuronosyl transferase (UDP-GT) inhibited the formation of SN-38G leading to a 270% AUC for SN-38 from subsequently-administered **CPT-11**. Thus, use of valproic acid, within the scope of the invention when pre-targeting DTPA-**carboxylesterase** to tumor, will also lead to higher levels of SN-38 at the target.

ORPL:
Potter, et al. "Isolation and Partial Characterization of a cDNA Encoding a Rabbit Liver **Carboxylesterase** That Activates the Prodrug Irinotecan (**CPT-11**)" Cancer Res., 58:2646-2651, 1998.

ORPL:
Potter, et al. "Cellular Localization Domains of a Rabbit and Human **Carboxylesterase:** Influence on Irinotecan (**CPT-11**) Metabolism by the Rabbit Enzyme" Cancer Res., 58:3627-3632, 1998.

ORPL:
Hiromitsu Takayama et al., "Synthesis of a New Class of **Camptothecin** Derivatives, The Long-Chain Fatty Acid Esters of 10-Hydroxycampothecin, As A Potent Prodrug Candidate, and Their In Vitro Metabolic Conversion By **Carboxylesterases**", Bioorganic & Medicinal Chemistry Letters, Oxford, Great Britain, vol. 8, No. 5, (Mar. 3, 1998), (415-418).

ORPL:
XP-000867715 Mary K. Danks et al., "Comparison of Activation of **CPT-11** By Rabbit and Human **Carboxylesterases** for Use in Enzyme/Prodrug Therapy", Clinical Cancer Research, (Apr. 1999), 5(4), (917-924).

US-PAT-NO: 6350756
DOCUMENT-IDENTIFIER: US 6350756 B1
TITLE: Camptothecin derivatives
DATE-ISSUED: February 26, 2002
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yang; Li-Xi	San Francisco	CA	N/A	N/A
Pan; Xiandao	San Francisco	CA	N/A	N/A
Wang; Huijuan	San Francisco	CA	N/A	N/A

US-CL-CURRENT: 514/283,514/279 ,544/361 ,546/14 ,546/41 ,546/48
ABSTRACT:
(20S) esters of camptothecin analogs are provided. The compounds are (20S) esters of an oxyalkanoic acid and camptothecin, which is optionally substituted at the 7, 9, 10, 11, and 12 positions of the camptothecin ring. The compounds are useful for treating cancer.
54 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: March 1, 2001

---------- KWIC ---------

ORPL:
Takayama, Hiromitsu et al., "Synthesis of a New Class of **Camptothecin** Derivatives, the Long-Chain Fatty Acid Esters Of 10-Hydroxycamptothecin, as a Potent Prodrug Candidate, and their In Vitro Metabolic Conversion by **Carboxylesterases**," Bioorganic & Medicinal Chemistry Letters 8, pp. 415-418.

US-PAT-NO: 6242457
DOCUMENT-IDENTIFIER: US 6242457 B1
TITLE: Camptothecin derivatives having antitumor activity
DATE-ISSUED: June 5, 2001
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Penco; Sergio	Milan	N/A	N/A	ITX
Merlini; Lucio	Milan	N/A	N/A	ITX
Carminati; Paolo	Pomezia	N/A	N/A	ITX
Zunino; Franco	Milan	N/A	N/A	ITX

US-CL-CURRENT: 514/283,514/280 ,546/48
ABSTRACT:

Camptothecin derivatives of camptothecin of formula (I) ##STR1##

wherein the groups R.sub.1, R.sub.2 and R.sub.3 are as defined in the description are disclosed.

The compounds of formula (I) are endowed with antitumor activity and show a good therapeutic index.

Processes for the preparation of the compounds of formula (I) and their use in the preparation of medicaments useful in the treatment of tumors, viral infections and antiplasmodium falciparum are also disclosed.
17 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: February 22, 2000

---------- KWIC ---------

BSPR:
Water-soluble Irinotecan was approved for the treatment of many solid tumors and ascites (colon-rectum, skin, stomach, breast, small and non-small cell lung, cervix and ovarian cancer and in non-Hodgkin lymphoma). Moreover, Irinotecan resulted active in solid tumors resistant to Topotecan, vincristine or melphalan and MDR-1 cells resulted marginally resistant to the drug. The active metabolite was identified as the 10-hydroxyderivatives (SN-38), produced by the action of **carboxylesterases**. **CPT-11** showed a good activity using different administration routes, such as intraperitoneal, intravenous, oral (Costin D., Potmhexyl M. Advances in Pharmacol. 29B, 51-72 1994).

BSPR:
In fact, it was observed that some resistant tumour cells contain mutant forms of topo I, accordingly the formation of the topo I-DNA complex is damaged or some cells lack in the **carboxylesterase** activity, necessary for converting **CPT-11** in the active metabolite SN-38 and are thus resistant against this drug (Rothenberg, 1997, ibid.).

US-PAT-NO: 6228855
DOCUMENT-IDENTIFIER: US 6228855 B1
TITLE: Aromatic esters of camptothecins and methods to treat cancers
DATE-ISSUED: May 8, 2001
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cao; Zhisong	Friendswood	TX	N/A	N/A
Giovanella; Beppino C.	Houston	TX	N/A	N/A

US-CL-CURRENT: 514/224.2,514/185 ,546/48 ,546/50 ,546/51
ABSTRACT:
Aromatic camptothecin ester compounds having the formula: ##STR1##

are described as well as formulations containing the compounds. Methods of treating cancer and/or tumors are also disclosed.
107 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: August 3, 1999

---------- KWIC ---------

BSPR:
Conversion of the prodrugs to camptothecins is mediated by a group of enzymes called esterases. Mammalian **carboxylesterases** represent a multigene family and are present in a wide variety of organs and tissues of many mammalian species (Satoh, in reviews in Biochemical Toxicology, 8:155-81, New York: Elsevier, 1987; Heymann, in Enzymatic Basis of Detoxication, 2:291-323, New York: Academic, 1980, and in Metabolic Basis of Detoxication, 1:229-45, New York: Academic, 1982). In general, the highest hydrolase activity occurs in the liver. **Carboxylesterase** activity is present in many tissues in addition to liver. More information about distribution of **carboxylesterases** in tissues can be found in a review article written by Satoh et al. (Annu. Rev. Pharmacol. Toxicol. 38, 257, 1998). **Carboxylesterases** are known to be responsible for the hydrolysis of many exogenous compounds, the consequences of which include both activation of prodrugs and deactivation of drugs. **CPT-11,** a semisynthetic **camptothecin** derivative and now commercially available for cancer treatment, is a prodrug of SN-38. This compound is converted to SN-38 by **carboxylesterases** (Danks et al., Cancer Res. 58, 20, 1998; Potter et al., Cancer Res. 58, 2646, 1998; Tsuji et al., J. Pharmacobio-Dyn. 14, 341, 1991). The prodrugs disclosed by the present invention are rapidly distributed throughout the body within a short period of time after delivery and are then converted to active **camptothecin** compounds by **carboxylesterases** specifically in tissues.

US-PAT-NO: 6217860
DOCUMENT-IDENTIFIER: US 6217860 B1
TITLE: Gene therapy for solid tumors, papillomas and warts
DATE-ISSUED: April 17, 2001
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Woo; Savio L. C.	Houston	TX	N/A	N/A
Chen; Shu-Hsia	Houston	TX	N/A	N/A

US-CL-CURRENT: 424/93.2,424/93.6 ,435/320.1 ,514/44
ABSTRACT:

The present invention provides a novel method of treating localized solid tumors (metastatic carcinomas, papilloma and warts) in an individual. The method comprises delivering a suicide gene, by way of a recombinant adenoviral vector or other DNA transport system, into the solid tumor. Subsequently, a prodrug, such as the drug ganciclovir, is administered to the individual. The methods of the present invention may used to treat several different types of solid tumors including papillomas, warts, colon carcinoma, prostate cancer, breast cancer, lung cancer, melanoma, hepatoma, brain lymphoma and head and neck cancer.

29 Claims, 23 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 27

DATE FILED: September 24, 1999

---------- KWIC ---------

ORPL:
Kojima, A. et al.; In vivo human **carboxylesterase** cDNA gene transfer to activate the prodrug **CPT-11** for local treatment of solid tumors; J. Clin. Invest.; 101(8):1789-96 (1998).

US-PAT-NO: 6194579
DOCUMENT-IDENTIFIER: US 6194579 B1
TITLE: Highly lipophilic camptothecin derivatives
DATE-ISSUED: February 27, 2001
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	Boerne	TX	N/A	N/A

US-CL-CURRENT: 546/48
ABSTRACT:

Novel compounds, formulations and methods of treating patients with cancer are provided for in this invention. The compounds are derivatives of camptothecin, and specifically relate to compounds having novel substitutions at the C-7 position of the camptothecin scaffold B-ring. The formula I compounds are highly lipophilic, lactone stable, do not require metabolic activation, and are potent antineoplastic compounds.
5 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: December 23, 1999

---------- KWIC ---------

BSPR:
Of this diverse group of substituted CPT derivatives undergoing human clinical development, Irinotecan (**CPT-11**) has been one of the most extensively studied in Phase I and Phase II clinical trials in human patients with cancer. It is noteworthy that Irinotecan, which is a water soluble prodrug, is biologically inactive and requires activation by a putative **carboxylesterase** enzyme. The active species of Irinotecan is the depiperidenylated 10-hydroxy-7-ethyl **camptothecin** (claimed in Miyasaka et al. U.S. Pat. No. 4,473,692 (1984)), which is also known as SN38. SN38 is a toxic lipophilic metabolite which is formed by an in vivo bioactivation of Irinotecan by a putative **carboxylesterase** enzyme.

US-PAT-NO: 6169080
DOCUMENT-IDENTIFIER: US 6169080 B1
TITLE: Highly lipophilic camptothecin derivatives
DATE-ISSUED: January 2, 2001
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	Boerne	TX	N/A	N/A
Haridas; Kochat	San Antonio	TX	N/A	N/A
Seetharamulu; P.	San Antonio	TX	N/A	N/A
Reddy; Dasharatha G.	San Antonio	TX	N/A	N/A
Yao; Shijie	San Antonio	TX	N/A	N/A
Petluru; Pavankumar	San Antonio	TX	N/A	N/A
N.V.	San Antonio	TX	N/A	N/A
Murali; Dhanabalan				

US-CL-CURRENT: 514/63,514/283 ,546/14 ,546/48
ABSTRACT:
This invention relates to novel derivatives of camptothecin, and will, particularly to derivatives having a substitution at the C-7 position, or at one of the C-9, C-10, C-11 or C-12 positions, or to disubstituted derivatives having a first substitution at C-7 and a second at one of C-9, C-10, C-11 or C-12. The invention also includes methods of using the compounds as Topoisomerase I inhibitors to treat patients with cancer. The invention also includes pharmaceutical formulations which consist of the novel compounds in solution or suspension with one or more pharmaceutical excipients or dilutes.
10 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: February 11, 1998

---------- KWIC ---------

BSPR:
Of this diverse group of substituted **camptothecin** derivatives undergoing human clinical development, **CPT-11** is one of the most extensively studied in clinical trials in human patients with cancer. **CPT-11** (Irinotecan/Camptosar.RTM.) was approved for human use by the FDA in June, 1996. It is noteworthy that **CPT-11** is biologically inactive and requires activation by a putative **carboxylesterase** enzyme. The active species of **CPT-11** is the depiperidenylated 10-hydroxy 7-ethyl **camptothecin** (claimed in Miyasaka et al. U.S. Pat. No. 4,473,692 (1984)), also known as SN38. SN38 is a toxic lipophilic metabolite which results from in vivo bioactivation of **CPT-11 by a carboxylesterase** enzyme. SN38 is very poorly soluble in water and has not been directly administered to human patients with cancer. Recently it has been reported in human patients that SN38 undergoes further metabolism to form an inactive glucuronide species. The glucuronide species also appears to be involved in producing human toxicity (diarrhea and leukopenia are the major dose-limiting toxicities) and substantial interpatient variability in drug levels of the free metabolite and

its glucuronide. **CPT-11** has been studied in human clinical trials in the United States, Europe and Japan and several patient deaths due to drug toxicity have been reported in association with the use of **CPT-11**.

US-PAT-NO: 6159935
DOCUMENT-IDENTIFIER: US 6159935 A
TITLE: Method for preventing diarrhea
DATE-ISSUED: December 12, 2000
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Miller; Langdon L.	Lebanon	NJ	N/A	N/A
Rothermel; John David	Randolph	NJ	N/A	N/A
O'Dowd; Hugh Michael	Long Valley	NJ	N/A	N/A

US-CL-CURRENT: 514/12,514/283
ABSTRACT:

The present invention relates to a method for preventing irinotecan-induced or camptothecin-induced or camptothecin-analog-induced diarrhea by administering an effective amount of octreotide. In particular the invention concerns new methods, combination formulations and kits to prevent late diarrhea caused by irinotecan or camptothecin, or camptothecin-analog administration.

9 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: November 29, 1999

---------- KWIC ---------

DEPR:
Irinotecan is (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidino-piperidino)carbonyloxy]-1H-pyrano[3',4':6,7] indolizino [1,2-b]quinoline-3,14(4H,12H)dione. Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the empirical formula C.sub.33 H.sub.38 N.sub.4 O.sub.6 HC13H.sub.2 O and a molecular weight of 677.19. Irinotecan hydrochloride was clinically investigated as **CPT-11**. Irinotecan is a prodrug converted in vivo by plasma and tissue **carboxylesterases** to SN-38 (7-ethyl-10-hydroxy **camptothecin**), an active metabolite that is an inhibitor of the nuclear enzyme topoisomerase I. Irinotecan has shown activity against a variety of tumor types, and in particular, refractory colorectal tumors.

US-PAT-NO: 6028078
DOCUMENT-IDENTIFIER: US 6028078 A
TITLE: Highly lipophilic camptothecin derivatives
DATE-ISSUED: February 22, 2000
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	Boerne	TX	N/A	N/A
Petluru; Pavankumar V.	San Antonio	TX	N/A	N/A
Reddy; Dasharatha	San Antonio	TX	N/A	N/A
Murali; Dhanabalan	San Antonio	TX	N/A	N/A
Haridas; Kochat	San Antonio	TX	N/A	N/A
Seetharamulu; Peddaiahgari	San Antonio	TX	N/A	N/A
Yao; Shijie				

US-CL-CURRENT: 514/283,546/48
ABSTRACT:

Novel compounds, formulations and methods of treating patients with cancer are provided for in this invention. The compounds are derivatives of camptothecin, and specifically relate to compounds having novel substitutions at the C-7 position of the camptothecin scaffold B-ring. The formula I compounds are highly lipophilic, lactone stable, do not require metabolic activation, and are potent antineoplastic compounds.
13 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: October 26, 1998

---------- KWIC ---------

BSPR:
Of this diverse group of substituted CPT derivatives undergoing human clinical development, Irinotecan (**CPT-11**) has been one of the most extensively studied in Phase I and Phase II clinical trials in human patients with cancer. It is noteworthy that Irinotecan, which is a water soluble prodrug, is biologically inactive and requires activation by a putative **carboxylesterase** enzyme. The active species of Irinotecan is the depiperidenylated 10-hydroxy-7-ethyl **camptothecin** (claimed in Miyasaka et al. U.S. Pat. No. 4,473,692 (1984)), which is also known as SN38. SN38 is a toxic lipophilic metabolite which is formed by an in vivo bioactivation of Irinotecan by a putative **carboxylesterase** enzyme.

US-PAT-NO: 5958937
DOCUMENT-IDENTIFIER: US 5958937 A
TITLE: Pharmaceutical formulations of poorly water soluble camptothecin analogues and NMP
DATE-ISSUED: September 28, 1999
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	San Antonio	TX	N/A	N/A
Haridas; Kochat	San Antonio	TX	N/A	N/A
Murali; Dhanabalan	San Antonio	TX	N/A	N/A
Reddy; Dasharatha Gauravaram	San Antonio	TX	N/A	N/A

US-CL-CURRENT: 514/283,514/423
ABSTRACT:

A- and/or B-ring substituted camptothecin derivatives, which are poorly water soluble (less than 5 micrograms per milliliter of water), are highly lipophilic camptothecin derivatives (HLCD) and are very active against a variety of human cancers. Because of their very poor water solubility, HLCD have not been used to treat human patients with cancer due to the inability to administer sufficient quantities of the HLCD dissolved in a pharmaceutical formulation. This invention overcomes these limitations by teaching novel pharmaceutically acceptable HLCD formulations for the direct administration of HLCD to human patients with cancer. The claimed invention also describes the methods to create solutions of HLCD and antitumor compositions of HLCD to allow the administration of HLCD in sufficient amounts to treat human patients with various types of cancer. This invention is also directed to injectable sterile solutions, antitumor compositions, solutions and suspensions comprising N-methyl-2-pyrrolidinone and a highly lipophilic camptothecin derivative.
25 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: October 22, 1997

---------- KWIC ---------

DEPR:
Kanzawa F, et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552; 1992.

ORPL:
Kanzawa, F. et al., Role of **Carboxylesterase** on Metabolism of Campthothecin Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells; Proceedings of the American Association for Cancer Research, 33:A2552, (1992).

US-PAT-NO: 5955467
DOCUMENT-IDENTIFIER: US 5955467 A
TITLE: Pharmaceutical formulations of poorly water soluble camptothecin analogues and NMP
DATE-ISSUED: September 21, 1999
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	San Antonio	TX	N/A	N/A
Haridas; Kochat	San Antonio	TX	N/A	N/A
Murali; Dhanabalan	San Antonio	TX	N/A	N/A
Reddy; Dasharatha Gauravaram	San Antonio	TX	N/A	N/A

US-CL-CURRENT: 514/283,514/423
ABSTRACT:

A- and/or B-ring substituted camptothecin derivatives, which are poorly water soluble (less than 5 micrograms per milliliter of water), are highly lipophilic camptothecin derivatives (HLCD) and are very active against a variety of human cancers. Because of their very poor water solubility, HLCD have not been used to treat human patients with cancer due to the inability to administer sufficient quantities of the HLCD dissolved in a pharmaceutical formulation. This invention overcomes these limitations by teaching novel pharmaceutically acceptable HLCD formulations for the direct administration of HLCD to human patients with cancer. The claimed invention also describes the methods to create solutions of HLCD and antitumor compositions of HLCD to allow the administration of HLCD in sufficient amounts to treat human patients with various types of cancer. This invention is also directed to injectable sterile solutions, antitumor compositions, solutions and suspensions comprising N-methyl-2-pyrrolidinone and a highly lipophilic camptothecin derivative.
25 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: October 22, 1997

---------- KWIC ---------

DEPR:
Kanzawa F, et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552; 1992.

ORPL:
Kanzawa, F. et al., Role of **Carboxylesterase** on Metabolism of Campthothecin Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells; Proceedings of the American Association for Cancer Research, 33:A2552, (1992).

US-PAT-NO: 5935967
DOCUMENT-IDENTIFIER: US 5935967 A
TITLE: Pharmaceutical formulations of highly lipophilic camptothecin derivatives
DATE-ISSUED: August 10, 1999
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	Boerne	TX	N/A	N/A
Haridas; Kochat	San Antonio	TX	N/A	N/A
Murali; Dhanabalan	San Antonio	TX	N/A	N/A
Reddy; Dasharatha Gauravaram	San Antonio	TX	N/A	N/A

US-CL-CURRENT: 514/283,514/423
ABSTRACT:
Pharmaceutical formulations of highly lipophilic, poorly water soluble derivatives of Camptothecin are disclosed. The formulations include an effective amount of the HLCD dissolved or suspended in an appropriate amount of N-methyl-2-pyrrolidinone (NMP), and one or more pharmaceutically acceptable excipients.
8 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: January 20, 1998

---------- KWIC ---------

BSPR:
CPT-11 is a water soluble prodrug for the highly active, highly toxic, highly lipophilic CPT derivative, SN38 (10-hydroxy-7-ethyl-CPT). **CPT-11** is an inactive compound, and requires activation by a putative **carboxylesterase** enzyme to the active SN38 species. It is also known that SN38 can undergo an additional glucuronidation reaction, in vivo, and that the SN38-glucuronide species may be highly toxic to normal, healthy cells, and has little antitumor activity.

US-PAT-NO: 5910491
DOCUMENT-IDENTIFIER: US 5910491 A
TITLE: Highly lipophilic camptothecin derivatives
DATE-ISSUED: June 8, 1999
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	Boerne	TX	N/A	N/A
Petluru; Pavankumar	San Antonio	TX	N/A	N/A
N.V.	San Antonio	TX	N/A	N/A
Reddy; Dasharatha	San Antonio	TX	N/A	N/A
Murali; Dhanabalan	San Antonio	TX	N/A	N/A
Haridas; Kochat	San Antonio	TX	N/A	N/A
Seetharamulu; Peddaiahgari	San Antonio	TX	N/A	N/A
Yao; Shijie				

US-CL-CURRENT: 514/63,514/283 ,544/238 ,546/14 ,546/48
ABSTRACT:
Novel compounds, formulations and methods of treating patients with cancer are provided for in this invention. The compounds are derivatives of camptothecin, and specifically relate to compounds having novel substitutions at the C-7 position of the camptothecin scaffold B-ring. The formula I compounds are highly lipophilic, lactone stable, do not require metabolic activation, and are potent antineoplastic compounds.
14 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: August 19, 1997

---------- KWIC ---------

BSPR:
Of this diverse group of substituted CPT derivatives undergoing human clinical development, Irinotecan (**CPT-11**) has been one of the most extensively studied in Phase I and Phase II clinical trials in human patients with cancer. It is noteworthy that Irinotecan, which is a water soluble prodrug, is biologically inactive and requires activation by a putative **carboxylesterase** enzyme. The active species of Irinotecan is the depiperidenylated 10-hydroxy-7-ethyl **camptothecin** (claimed in Miyasaka et al. U.S. Pat. No. 4,473,692 (1984)), which is also known as SN38. SN38 is a toxic lipophilic metabolite which is formed by an in vivo bioactivation of Irinotecan by a putative **carboxylesterase** enzyme.

US-PAT-NO: 5900419
DOCUMENT-IDENTIFIER: US 5900419 A
TITLE: Formulations and compositions of poorly water soluble camptothecin derivatives
DATE-ISSUED: May 4, 1999
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	San Antonio	TX	N/A	N/A
Haridas; Kochat	San Antonio	TX	N/A	N/A
Murali; Dhanabalan	San Antonio	TX	N/A	N/A
Reddy; Dasharatha Gauravaram	San Antonio	TX	N/A	N/A

US-CL-CURRENT: 514/283,514/423
ABSTRACT:

A- and/or B-ring substituted camptothecin derivatives, which are poorly water soluble (less than 5 micrograms per milliliter of water), are highly lipophilic camptothecin derivatives (HLCD) and are very active against a variety of human cancers. Because of their very poor water solubility, HLCD have not been used to treat human patients with cancer due to the inability to administer sufficient quantities of the HLCD dissolved in a pharmaceutical formulation. This invention overcomes these limitations by teaching novel pharmaceutically acceptable HLCD formulations for the direct administration of HLCD to human patients with cancer. The claimed invention also describes the methods to create solutions of HLCD and antitumor compositions of HLCD to allow the administration of HLCD in sufficient amounts to treat human patients with various types of cancer. This invention is also directed to injectable sterile solutions, antitumor compositions, solutions and suspensions comprising N-methyl-2-pyrrolidinone and a highly lipophilic camptothecin derivative.
16 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: October 22, 1997

---------- KWIC ---------

DEPU:
Kanzawa F, et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552; 1992.

US-PAT-NO: 5880133
DOCUMENT-IDENTIFIER: US 5880133 A
TITLE: Pharmaceutical formulations of highly lipophilic camptothecin derivatives
DATE-ISSUED: March 9, 1999
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	San Antonio	TX	N/A	N/A
Haridas; Kochat	San Antonio	TX	N/A	N/A
Murali; Dhanabalan	San Antonio	TX	N/A	N/A
Reddy; Dasharatha Gauravaram	San Antonio	TX	N/A	N/A

US-CL-CURRENT: 514/283
ABSTRACT:
Pharmaceutical formulations of Highly Lipophilic Camptothecin Derivatives (HLCD) include HLCD dissolved in N-methyl Pyrrolidinene (NMP). The formulations also include quantities of pharmaceutically acceptable excipients and diluents incorporated thereinto.
12 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: June 21, 1996

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ORPL:
Kanzawa, F., et al., Role of **Carboxylesterase** on Metaolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552; 1992.

US-PAT-NO: 5859023
DOCUMENT-IDENTIFIER: US 5859023 A
TITLE: Formulations and compositions of poorly water soluble camptothecin derivatives
DATE-ISSUED: January 12, 1999
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	San Antonio	TX	N/A	N/A
Haridas; Kochat	San Antonio	TX	N/A	N/A
Murali; Dhanabalan	San Antonio	TX	N/A	N/A
Reddy; Dasharatha Gauravaram	San Antonio	TX	N/A	N/A

US-CL-CURRENT: 514/283,514/423
ABSTRACT:

A- and/or B-ring substituted camptothecin derivatives, which are poorly water soluble (less than 5 micrograms per milliliter of water), are highly lipophilic camptothecin derivatives (HLCD) and are very active against a variety of human cancers. Because of their very poor water solubility, HLCD have not been used to treat human patients with cancer due to the inability to administer sufficient quantities of the HLCD dissolved in a pharmaceutical formulation. This invention overcomes these limitations by teaching novel pharmaceutically acceptable HLCD formulations for the direct administration of HLCD to human patients with cancer. The claimed invention also describes the methods to create solutions of HLCD and antitumor compositions of HLCD to allow the administration of HLCD in sufficient amounts to treat human patients with various types of cancer. This invention is also directed to injectable sterile solutions, antitumor compositions, solutions and suspensions comprising N-methyl-2-pyrrolidinone and a highly lipophilic camptothecin derivative.
13 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: October 22, 1997

---------- KWIC ---------

DEPR:
Kanzawa F., et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552; 1992.

US-PAT-NO: 5859022
DOCUMENT-IDENTIFIER: US 5859022 A
TITLE: Formulations and compositions of poorly water soluble camptothecin derivatives
DATE-ISSUED: January 12, 1999
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	San Antonio	TX	N/A	N/A
Haridas; Kochat	San Antonio	TX	N/A	N/A
Murali; Dhanabalan	San Antonio	TX	N/A	N/A
Reddy; Dasharatha Gauravaram	San Antonio	TX	N/A	N/A

US-CL-CURRENT: 514/283,514/423
ABSTRACT:

A- and/or B-ring substituted camptothecin derivatives, which are poorly water soluble (less than 5 micrograms per milliliter of water), are highly lipophilic camptothecin derivatives (HLCD) and are very active against a variety of human cancers. Because of their very poor water solubility, HLCD have not been used to treat human patients with cancer due to the inability to administer sufficient quantities of the HLCD dissolved in a pharmaceutical formulation. This invention overcomes these limitations by teaching novel pharmaceutically acceptable HLCD formulations for the direct administration of HLCD to human patients with cancer. The claimed invention also describes the methods to create solutions of HLCD and antitumor compositions of HLCD to allow the administration of HLCD in sufficient amounts to treat human patients with various types of cancer. This invention is also directed to injectable sterile solutions, antitumor compositions, solutions and suspensions comprising N-methyl-2-pyrrolidinone and a highly lipophilic camptothecin derivative.
25 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: October 22, 1997

---------- KWIC ---------

DEPU:
Kanzawa F., et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552; 1992.

US-PAT-NO: 5726181
DOCUMENT-IDENTIFIER: US 5726181 A
TITLE: Formulations and compositions of poorly water soluble camptothecin derivatives
DATE-ISSUED: March 10, 1998
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	San Antonio	TX	N/A	N/A
Haridas; Kochat	San Antonio	TX	N/A	N/A
Murali; Dhanabalan	San Antonio	TX	N/A	N/A
Reddy; Dasharatha Gauravaram	San Antonio	TX	N/A	N/A

US-CL-CURRENT: 514/283,514/423
ABSTRACT:

A- and/or B-ring substituted camptothecin derivatives, which are poorly water soluble (less than 5 micrograms per milliliter of water), are highly lipophilic camptothecin derivatives (HLCD) and are very active against a variety of human cancers. Because of their very poor water solubility, HLCD have not been used to treat human patients with cancer due to the inability to administer sufficient quantities of the HLCD dissolved in a pharmaceutical formulation. This invention overcomes these limitations by teaching novel pharmaceutically acceptable HLCD formulations for the direct administration of HLCD to human patients with cancer. The claimed invention also describes the methods to create solutions of HLCD and antitumor compositions of HLCD to allow the administration of HLCD in sufficient amounts to treat human patients with various types of cancer. This invention is also directed to injectable sterile solutions, antitumor compositions, solutions and suspensions comprising N-methyl-2-pyrrolidinone and a highly lipophilic camptothecin derivative.
21 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: June 5, 1995

---------- KWIC ---------

DEPR:
Kanzawa F., et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552; 1992.

ORPL:
Kanzawa, F. et al., Role of **Carboxylesterase** on Metabolism of Campthothecin Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells; Proceedings of the American Association for Cancer Research, 33:A2552, (1992).

US-PAT-NO: 5674874
DOCUMENT-IDENTIFIER: US 5674874 A
TITLE: Lactone stable formulation of 7-ethyl 10-hydroxy camptothecin and methods for uses thereof
DATE-ISSUED: October 7, 1997
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	San Antonio	TX	N/A	N/A
Haridas; Kochat	San Antonio	TX	N/A	N/A

US-CL-CURRENT: 514/283
ABSTRACT:

7-ethyl-10-hydroxy camptothecin (HECPT), an active metabolite of the camptothecin analog CPT-11 which is used as an anticancer drug, is poorly soluble in water. Because of its poor water solubility, HECPT has not been directly administered by parenteral or oral routes in human patients for the purpose of inhibiting the growth of cancer cells. There is also unpredictable interpatient variability in the metabolic production of HECPT from CPT-11 which limits the utility of CPT-11. This invention overcomes these limitations by teaching novel pharmaceutically acceptable lactone stable HECPT formulations for the direct administration of lactone stable HECPT formulations orally or parenterally to patients with various forms of cancer.

9 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: September 1, 1995

---------- KWIC ---------

BSPR:

Of this diverse group of substituted **camptothecin** derivatives undergoing human clinical development, **CPT-11** is one of the most extensively studied in Phase I and Phase II clinical trials in human patients with cancer. It is noteworthy that **CPT-11,** which is a water soluble prodrug, is biologically inactive and requires activation by a putative **carboxylesterase** enzyme. The active species of **CPT-11** is the depiperidenylated 7-ethyl-10-hydroxy **camptothecin,** also known as SN38 (claimed in Miyasaka et al. U.S. Pat. No. 4,473,692 (1984)), which is also described as HECPT for the purposes of this invention. SN38 is a toxic lipophilic metabolite which results from in vivo bioactivation of **CPT-11 by a carboxylesterase** enzyme. SN38 is very poorly soluble in water and has not been directly administered to human patients with cancer. Recently it has been reported in human patients that SN38 undergoes further metabolism to form a glucuronide species which is an inactive form of the drug with respect to antitumor activity, and also appears to be involved in producing human toxicity (diarrhea, leukopenia) and substantial interpatient variability in drug levels of the free metabolite and its glucuronide.

DEPR:

Kanzawa F, et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 and C-9 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552; 1992.

US-PAT-NO: 5674873
DOCUMENT-IDENTIFIER: US 5674873 A
TITLE: Lactone stable formulation of 10-hydroxy 7-ethyl camptothecin and methods for uses thereof
DATE-ISSUED: October 7, 1997
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	San Antonio	TX	N/A	N/A
Haridas; Kochat	San Antonio	TX	N/A	N/A

US-CL-CURRENT: 514/283
ABSTRACT:

10-hydroxy 7-ethyl camptothecin (HECPT), an active metabolite of the camptothecin analog CPT-11, is poorly soluble in water. Because of its poor water solubility, HECPT has not been directly administered by parenteral or oral routes in human patients for the purpose of inhibiting the growth of cancer cells. There is also unpredictable interpatient variability in the metabolic production of HECPT from CPT-11 which limits the utility of CPT-11. This invention overcomes these limitations by teaching novel pharmaceutically acceptable lactone stable HECPT formulations for the direct administration of HECPT. The claimed invention also describes novel dosages, schedules, and routes of administration of the lactone stable HECPT formulations to patients with various forms of cancer.

30 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: June 7, 1995

---------- KWIC ---------

DEPR:
Kanzawa F., et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Pan. Assoc. Cancer Res. 33:A2552; 1992.

ORPL:
Kanzawa, F., et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33: A2552, 1992.

US-PAT-NO: 5633260
DOCUMENT-IDENTIFIER: US 5633260 A
TITLE: 11,7 Substituted camptothecin derivatives and formulations of 11,7 substituted camptothecin derivatives and methods for uses thereof
DATE-ISSUED: May 27, 1997
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	San Antonio	TX	N/A	N/A
Haridas; Kochat	Houston	TX	N/A	N/A

US-CL-CURRENT: 514/283
ABSTRACT:

The novel compounds 11-hydroxy-7-ethyl camptothecin and 11-hydroxy-7-methoxy camptothecin (11,7-HECPT and 11,7-HMCPT) are active anticancer compounds which are poorly soluble in water. Because of their novelty, 11,7-HECPT and 11,7-HMCPT derivatives have not been directly administered by parenteral or oral routes to human subjects as an antitumor composition for the purpose of inhibiting the growth of cancer cells. The claimed compositions are useful as compared to the water soluble camptothecin derivatives, such as CPT-11, in clinical trials. The unpredictable interpatient variability in the metabolic production of an active metabolite from CPT-11 limits the utility of CPT-11. This invention overcomes these limitations by claiming novel pharmaceutically acceptable lactone stable formulations of 11,7-HECPT or 11,7-HMCPT, to directly administer to patients. The present invention also claims 11,7-HECPT and 11,7-HMCPT compositions, the synthesis of 11,7-HECPT or 11,7-HMCPT, the methods of formulation of 11,7-HECPT or 11,7 -HMCPT, and the methods of use of 11,7-HECPT or 11,7-HMCPT. Additionally, the claimed invention is directed to novel dosages, schedules, and routes of administration for both the 11,7-HECPT or 11,7-HMCPT formulations to humans with various forms of cancer. Other embodiments of this invention include isolation methods and methods of synthesis of certain camptothecin derivatives.

42 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: August 24, 1995

---------- KWIC ---------

DEPR:
Kanzawa F. et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552, 1992.

US-PAT-NO: 5604233
DOCUMENT-IDENTIFIER: US 5604233 A
TITLE: Lactone stable formulation of 7-ethyl camptothecin and methods for uses thereof
DATE-ISSUED: February 18, 1997
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	San Antonio	TX	N/A	N/A
Haridas; Kochat	Houston	TX	N/A	N/A

US-CL-CURRENT: 514/283
ABSTRACT:

7-ethyl camptothecin (ECPT), an active metabolite of the camptothecin analog CPT-11, is poorly soluble in water. Because of its poor water solubility, ECPT has not been directly administered by parenteral or oral routes in human patients for the purpose of inhibiting the growth of cancer cells. There is also unpredictable interpatient variability in the metabolic production of ECPT from CPT-11 which limits the utility of CPT-11. This invention overcomes these limitations by teaching novel pharmaceutically acceptable lactone stable ECPT formulations for the direct administration of ECPT. The claimed invention also describes novel dosages, schedules, and routes of administration of the lactone stable ECPT formulations to patients with various forms of cancer.
39 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: April 28, 1994

---------- KWIC ---------

DEPR:
Kanzawa F, et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552; 1992.

ORPL:
Kanzawa F. et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract): Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552, 1992.

US-PAT-NO: 5597829
DOCUMENT-IDENTIFIER: US 5597829 A
TITLE: Lactone stable formulation of camptothecin and methods for uses thereof
DATE-ISSUED: January 28, 1997
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	San Antonio	TX	N/A	N/A
Haridas; Kochat	Houston	TX	N/A	N/A

US-CL-CURRENT: 514/283
ABSTRACT:
Camptothecin (CPT) an anticancer drug is poorly soluble in water. This invention overcomes this limitation by teaching novel pharmaceutically acceptable lactone stable CPT formulations for the direct administration of CPT to human subjects with cancer. The claimed invention also describes novel dosages, schedules, and routes of administration of the lactone stable CPT formulations to patients with various forms of cancer.
39 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: May 9, 1994

---------- KWIC ---------

DEPR:
Kanzawa F., et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552; 1992.

US-PAT-NO: 5468754
DOCUMENT-IDENTIFIER: US 5468754 A
TITLE: 11,7 substituted camptothecin derivatives and formulations of 11,7 substituted camptothecin derivatives and methods for uses thereof
DATE-ISSUED: November 21, 1995
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	San Antonio	TX	N/A	N/A
Haridas; Kochat	Houston	TX	N/A	N/A

US-CL-CURRENT: 514/283,546/48
ABSTRACT:

The novel compounds 11-hydroxy-7-ethyl camptothecin and 11-hydroxy-7-methoxy camptothecin (11,7-HECPT and 11,7-HMCPT) are active anticancer compounds which are poorly soluble in water. Because of their novelty, 11,7-HECPT and 11,7-HMCPT derivatives have not been directly administered by parenteral or oral routes to human subjects as an antitumor composition for the purpose of inhibiting the growth of cancer cells. The claimed compositions are useful as compared to the water soluble camptothecin derivatives, such as CPT-11, in clinical trials. The unpredictable interpatient variability in the metabolic production of an active metabolite from CPT-11 limits the utility of CPT-11. This invention overcomes these limitations by claiming novel pharmaceutically acceptable lactone stable formulations of 11,7-HECPT or 11,7-HMCPT, to directly administer to patients. The present invention also claims 11,7-HECPT and 11,7-HMCPT compositions, the synthesis of 11,7-HECPT or 11,7-HMCPT, the methods of formulation of 11,7-HECPT or 11,7-HMCPT, and the methods of use of 11,7-HECPT or 11,7-HMCPT. Additionally, the claimed invention is directed to novel dosages, schedules, and routes of administration for both the 11,7-HECPT or 11,7-HMCPT formulations to humans with various forms of cancer. Other embodiments of this invention include isolation methods and methods of synthesis of certain camptothecin derivatives.

36 Claims, 0 Drawing figures
Exemplary Claim Number: 1

DATE FILED: April 19, 1994

---------- KWIC ---------

DEPU:
Kanzawa F. et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552, 1992.

ORPL:
Kanzawa F. et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552, 1992.

US-PAT-NO: 5447936
DOCUMENT-IDENTIFIER: US 5447936 A
TITLE: Lactone stable formulation of 10-hydroxy 7-ethyl camptothecin and methods for uses thereof
DATE-ISSUED: September 5, 1995
INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hausheer; Frederick H.	San Antonio	TX	N/A	N/A
Haridas; Kochat	San Antonio	TX	N/A	N/A

US-CL-CURRENT: 514/283
ABSTRACT:

10-hydroxy 7-ethyl camptothecin (HECPT), an active metabolite of the camptothecin analog CPT-11, is poorly soluble in water. Because of its poor water solubility, HECPT has not been directly administered by parenteral or oral routes in human patients for the purpose of inhibiting the growth of cancer cells. There is also unpredictable interpatient variability in the metabolic production of HECPT from CPT-11 which limits the utility of CPT-11. This invention overcomes these limitations by teaching novel pharmaceutically acceptable lactone stable HECPT formulations for the direct administration of HECPT. The claimed invention also describes novel dosages, schedules, and routes of administration of the lactone stable HECPT formulations to patients with various forms of cancer.
22 Claims, 0 Drawing figures
Exemplary Claim Number: 1

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DEPR:
Kanzawa F, et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract). Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552; 1992.

ORPL:
Kanzawa F. et al., Role of **Carboxylesterase** on Metabolism of **Camptothecin** Analog (**CPT-11**) in Non-Small Cell Lung Cancer Cell Line PC-7 Cells (Meeting Abstract), Proc. Annual Meet. Am. Assoc. Cancer Res. 33:A2552, 1992.